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EXAMINER
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ART UNIT	PAPER NUMBER
1644	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/674,857	ARMOUR ET AL.	
	Examiner	Art Unit	
	" Neon" Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/7/00; 4/8/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *16-29 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/07/00* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4-5, 16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 1-31 are pending.

2. Applicant's election with traverse of Group II, Claims 1-15 and 30, drawn to a recombinant polypeptide comprising a binding domain and an effector domain wherein the binding domain is the binding site of an antibody Fog1 capable of binding to RhD antigen on red blood cell and a pharmaceutical preparation, filed 4/8/02, is acknowledged. The traversal is on the grounds that (1) the present invention provides a binding molecule that minimizes undesirable activities such as CDC mediated by the IgG C domain while retaining desirable activities mediated by the IgG domain such as neonatal transport of IgG and inhibition of cellular response, (2) the invention is based on the use of chimeric antibody regions in which specific residues are altered, and these amino acids incorporated are selected only from IgG parent molecules, (3) the prior art Cole et al does not teach the combinations of functions required by the claims (e.g. FcγIIb binding) and does not teach the 2, 3 or 4 amino acids in at least 1 region of the C_H2 domain have been modified to the corresponding amino acids from a second amino acids from a second, different, human immunoglobulin heavy chain C_H2 domain. This is not found persuasive for following reasons: (1) applicants argue limitations not found in the base claim 1, for example, the binding specificity of the binding molecule, and the specific amino acid to be substitute in the specific regions of the human immunoglobulin heavy chain C_H2 domain. (2) Cole et al (of record, Immunology 159: 3613-3621, 1997; PTO 1449) teach a binding molecule which is a recombinant polypeptide comprising a binding domain capable of binding to a target molecule such as a T cell receptor and an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human heavy chain wherein the effector domain comprises a human immunoglobulin heavy chain of IgG2 having at least 2 amino acids at position 234 and 235 have been modified to V and A, respectively (See page 3615, Table 1, in particular). The said effector domain is capable of specifically binding to FcγIIb, and is derived from two or more human immunoglobulin heavy chain CH2 domains from IgG2, as recited in claims 1-3 (See page 3614, Materials and Methods, page 3617-3619, in particular). The said binding domain is the binding site of an antibody, which is capable of binding to a T cell receptor as recited in claims 13-14 (See entire document). Further, Greenwood *et al* teach a binding molecule such as chimeric recombinant antibodies DS1141, DS4414, DS4114 comprising (i) a binding domain capable of

binding a target molecule such as CAMPATH-1 antigen (CD52) and (ii) an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human immunoglobulin heavy chain wherein the reference binding molecule is capable of binding to the target molecule without significant complement mediated lysis or triggering cell mediated destruction of the target (ADCC) and the reference chimeric effector domain is derived from human immunoglobulin heavy chain CH2 domain from IgG1, and IgG4 (See Figs 1-4, in particular) and the reference chimeric effector domain includes Y to F at position 296. Greenwood *et al* teach the structural requirements for effector function of any antibody, which is located in the C-terminal half of the CH2 domain (residues 234, 238 and the hinge-link region from 300-331 (See page 1103, Fig 5, in particular). Greenwood *et al* teach four residues could be responsible for the failure of lack of ACDD: Tyr at 296 in IgG1 vs Phe in IgG4, Ala in 327 versus Gly in IgG4, Ala in 330 in IgG1 versus Ser in IgG4 and Pro at 331 in IgG1 to Ser in IgG4 (See Fig 5, page 1104, column 1, first full paragraph, in particular). The reference binding molecule wherein the first human immunoglobulin is IgG1 and the second human immunoglobulin is IgG4 (See Fig 1, in particular). The reference binding molecule wherein 2 amino acids in 1 region such as the C terminal half of the CH2 domain are modified to the corresponding amino acids from a second human immunoglobulin heavy CH2 domain such as IgG4 (See Fig 5, in particular).). The reference binding molecule wherein the effector domain shares at least about 90% identity with the wild type human immunoglobulin heavy chain CH2 domain since it has only one, two or maximum four mutations in the CH2 domain compared with the wild type. The reference binding molecule comprising a human immunoglobulin heavy chain CH2 domain having A at position 235, G position 327, S at position 330 and 331. (See Figs 1 and 5, in particular). The reference binding molecule comprising a human immunoglobulin heavy chain CH2 domain having a block of amino acids such as G position 327, S at position 330 and 331. (See Figs 1 and 5, in particular). The reference binding molecule wherein the binding domain is derived from a different source such as rat or chimeric humanized CAMPATH-1 antibodies to the effector domain (See page 1099, Materials and methods, in particular). The reference binding molecule is an antibody wherein the binding domain is capable of binding to platelet glycoprotein such as CAMPATH-1 (CD52) (See page 1099, Materials and methods, Introduction in particular). Greenwood *et al* teach further teach a pharmaceutical acceptable carrier such as IMDM for a pharmaceutical preparation comprising the reference binding molecule (See page 1099, column 2, ADCC, in particular). Greenwood *et al* teach IgG1 is the most potent isotype in ADCC, with

IgG3 somewhat less effective and IgG2 and IgG4 ineffective. The residues in the hinge-link region (233-238) are crucial to binding to the high affinity receptor FcγRI and the binding site for FcγRIII is overlapping this region (See page 1099, column 1, first paragraph, in particular). Thus, the reference teachings anticipate the claimed invention.

Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention. Further, a prior art search also requires a literature search. It is a burden to search more than one invention. Upon reconsideration, Group I, drawn to a recombinant polypeptide comprising a binding domain and an effector domain wherein the binding domain is CAMPATH-1 has been rejoined with Group II. Therefore, the requirement of Group II (now claims 1-15 and 30) and Groups III-XXI is still deemed proper and is therefore made FINAL.

3. Claims 16-29 and 31 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-15 and 30 drawn to a recombinant polypeptide comprising a binding domain and an effector domain wherein the binding domain is CAMPATH-1, and FOG-1 are being acted upon in this Office Action.

5. Applicant should amend the first line of the specification to reflect the relationship between the instant application and PCT/GB99/01441 filed 5/7/99 stated on the oath.

6. Claim 30 is objected to because it depends on non-elected claim 17. Further, Claim 30 is objected to under 37 CFR 1.75(c) as being in improper form because the claim references to two set of claims to different features. See MPEP § 608.01(n).

7. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

8. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The recitation of "chimeric effector domain" in claim 1 has no support in the specification as filed. The specification on page 6 discloses "chimeric polypeptides".

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-15 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a binding molecule which is a recombinant human immunoglobulin comprising (i) a binding domain capable of binding to a target molecule wherein the molecule is selected from the group consisting of RhD antigen (Fog-1) and CAMPATH-1 (CD52), (ii) an effector domain having an amino acid sequence substantially homologous to all or part of a constant domain of a human immunoglobulin heavy chain wherein the binding molecule is capable of binding to the target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target and whereby the effector domain is capable of specifically binding to FcRn and/or FcγRIIb, (2) the said binding molecule wherein the effector domain comprises an amino acid sequence substantially homologous to the C_H2 domain from human IgG1, IgG2 or IgG4, said sequence comprising one or more amino acid substitutions at position 233 from E to P, at position 234 from L to V, at position 235 from L to A, at position 327 from G to A, at position 330 from A to S and at position 331 from P to S, a deletion at position 236 or an addition of G at position 236 in accordance with the EU numbering system, (3) the said binding molecule wherein the effector domain shares at least 90% sequence identity with the human immunoglobulin heavy chain C_H2 domain, (4) the said binding molecule comprises a human immunoglobulin heavy chain C_H2 domain having one or more amino acids or deletions at the stated positions in accordance with the EU numbering system: P at position 233, V at position 234, A at position 235 and no residue at position 236; or P at position 233, V at position 234, A at position 235, G at position 236, and/or G at position 237, S at position 330, and S at position 331, (5) the said binding molecule wherein the effector domain is selected from the group consisting of SEQ ID NO: 1 (G1Δab), SEQ ID NO: 2 (G2Δa) and SEQ ID NO: 3 (G1Δac), (6) the said binding molecule further comprising modifications to render the said molecule substantially null

allotypic, (7) the said binding molecule wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis comparing with human immunoglobulin heavy chain CH2 domain, (8) the said binding molecule wherein the effector domain has retained an affinity for FcγRIIb, (9) the said binding domain molecule wherein the binding domain is selected from the group consisting of an antibody capable of binding specifically to RhD antigen on red blood cell (FOG-1) or CAMPATH-1 (CD52) for inhibiting monocyte activation and ADCC in vitro, **does not** reasonably provide enablement for (1) *any* binding molecule which is a recombinant polypeptide comprising (i) *any* binding domain capable of binding to any target molecule, and (ii) *any* effector domain having *any* amino acid sequence "substantially homologous to all or part" of *any* constant domain of a human immunoglobulin chain; wherein the binding molecule is capable of binding *any* target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target, characterized in that the effector domain is capable of specifically biding FcRn and/or FcγRIIb and *any* chimeric effector domain which is derived from *any* two or more human immunoglobulin heavy chain C_H2 domains including *any* first human immunoglobulin heavy chain C_H2 domain wherein *any* 2, 3 or 4 amino acids in at least 1 region of the C_H2 domain have been modified to the corresponding amino acids from *any* second, different, human immunoglobulin heavy chain C_H2 domain, wherein the region is selected from the 2 discrete regions numbered residues 233-236 and 327-331 in accordance with the EU numbering system, and wherein in each case the human immunoglobulin is selected from IgG1, IgG2, and IgG4, (2) *any* binding molecule mentioned above wherein the first human immunoglobulin is selected from IgG1, IgG2, and IgG4, and the second human immunoglobulin is selected from IgG2 and IgG4, (3) *any* binding molecule mentioned above wherein *any* two amino acids in 1 region of the C_H2 domain are modified to the corresponding amino acids from *any* second human immunoglobulin heavy chain C_H2 domain, (4) *any* binding molecule mentioned above wherein at least *any* two amino acids in each of the two discrete regions of the C_H2 domain are modified to the corresponding amino acids in the corresponding region in *any* second and *any* third human immunoglobulin heavy chain C_H2 domain respectively, (5) *any* binding molecule mentioned above wherein the effector domain shares at least "about 90% sequence identity" with *any* first human immunoglobulin heavy chain C_H2 domain, (6) *any* binding molecule mentioned above wherein comprising *any* human immunoglobulin heavy chain C_H2 domain having *any* one or more amino acids or deletions at the stated positions such as the ones recited in claims 6-7, (7)

any binding molecule mentioned above wherein the effector domain is selected from *any* G1Δab, *any* G2Δa or *any* G1Δac, (8) *any* binding molecule mentioned above further comprising modifications to render the molecule "substantially null allotypic", (9) *any* binding molecule mentioned above wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with *any* first or second human immunoglobulin heavy chain C_H2 domain, (10) *any* binding molecule mentioned above wherein the effector domain has retained an affinity for FcγRIIb, (11) *any* binding molecule mentioned above wherein the binding domain derives from any different source to the effector domain, (12) *any* binding molecule mentioned above wherein the binding domain is selected from the binding site of *any* antibody, any enzyme, *any* hormone, any receptor, *any* cytokine or *any* antigen any ligand or *any* adhesion molecule, (13) *any* binding molecule mentioned above wherein the binding site is *any* capable of *any* of binding to any RhD antigen, *any* HPA alloantigen of platelet, *any* neutrophil antigen, *any* T cell receptor, any integrin, *any* GMB collagen, *any* Der P1, *any* HPA-1a, *any* VAP-1, *any* laminin, *any* Lutheran, *any* platelet glycoprotein VI, *any* platelet glycoprotein Ia/IIa, and (14) *any* pharmaceutical preparation comprising *any* binding molecule mentioned above plus a pharmaceutically acceptable carrier for treating any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only binding molecules which are recombinant antibodies wherein each recombinant antibody comprises a binding domain capable of binding to CAMPATH-1 (CD52) or FOG-1 (RhD antigen on RBC) and variant of human IgG1 constant region which incorporate IgG2 residues in the region 233-236 and/or IgG4 residues at positions 327, 330 and 331 into the corresponding amino acid residues of IgG1 based on the European

Union numbering system. The first region comprises residues 233-236, which is part of the hinge link or lower hinge region of the C_H2 domain while the second region 327, 330 and 331 is the N-terminal end of the C_H2 domain. In the G1Δab mutation of SEQ ID NO: 1, the E at position 233 of IgG1 is substitute for P from IgG2, the L at position 234 of IgG1 is substitute for V from IgG2, the L at position 235 is substituted for A from IgG2, Since IgG2 has a deletion at 236 where the other class of IgG has G, the mutation at 236 is omitted (no residue) or G, the A at 327 of IgG1 is substitute for G from IgG4, The A at 330 of IgG1 is substitute for S from IgG4 and the P at 331 of IgG1 is substitute for S from IgG4. For the G2Δa mutation of SEQ ID NO: 2, E is changed to P at position 233, L to V at position 234, L to A at position 235, a deletion at position 236, A to G at position 327, A to S at position 330 and P to S at position 331. For G1Δac mutation of SEQ ID NO: 3, E is changed to P at position 233, L to V at position 234, L to A at position 235, G remains the same at position 236, A to G at position 327, A to S at position 330 and P to S at position 331. The said binding molecules wherein the effector domain of SEQ ID NO: 1, 2 and 3 has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1. The said binding molecules of SEQ ID NO: 1, 2 and 3 wherein the effector domain has retained an affinity for FcγRIIb.

Other than the specific binding molecule mentioned above wherein the binding domain is FOG-1 and CAMPATH-1 and the effector domain is selected from the group consisting of SEQ ID NO: 1, SEQ IN NO: 2 and SEQ ID NO: 3 for in vitro screening of the killing of PBMC by complement lysis with CAMMPATH-1 or the killing of RBD by ADCC with Fog-1 associated with fetal thrombocytopenia by way of assessing directly or indirectly through inability to trigger monocyte chemiluminescence, the specification does not teach how to make and use *any* binding molecules such as the ones recited in claims 1-15 for a pharmaceutical for treating *any* disease. Further, the term "substantially homologous to all or part of constant domain" in claim 1 is vague and indefinite. The specification on page 11 defines "substantially homologous" is meant that the amino acid sequence shares at least about 50 % or 60% or 70%, or 80% homology with the reference immunoglobulin. A 40% homology is about 50%, which translates to 60% differences. The specification as filed fails to teach which amino acid residues within the constant region of the human immunoglobulin selected from the group consisting of IgG1, IgG2 and IgG4 can tolerate changes such that having at least 50 to 60% difference would still maintain structure and desire functions such as inhibiting complement mediated lysis and binding to FcγRI, FcγRIIa or

FcγRIII. Even if the effector domain is "about 90% sequence identity" with any first human immunoglobulin heavy chain C_H2 domain as recited in claim 5, it is unpredictable which undisclosed amino acid residue within the CH2 domain could tolerate change.

Mogan *et al* (PTO 1449) teach changing the Leu235 to Glu in the N-terminal end of the C_H2 domain abolished FcγRI binding and unexpectedly also abolished human complement lysis while the Fc FcγRIII binding is retained (See entire document, page 320, column 1, first paragraph, in particular). The specification on page 55 lines 15-19 discloses that it should be stressed that **the effect of mutations cannot always be predicted** from wild type antibody activities, but will dependent on the novel context (based on mixed subclasses of IgG) in which the mutation is present.

Further, the said binding molecule comprising *any* binding domain capable of binding to *any* target molecule lacks specificity.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). Given the lack of guidance and working examples, predicting what changes can be made to the amino acid sequence in the binding domain (hypervariable region of the immunoglobulin) that after insertion and/or modification will retain both structure and have similar function is unpredictable. Furthermore, it is well known in the art at the time the invention was made that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimentional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular).

Kuby *et al* teach that immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide may result in **antibody specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the lack of binding specificity of the binding molecule, it is unpredictable which undisclosed binding molecule, which is a recombinant polypeptide, comprising any binding domain capable of binding to any target molecule and any effector domain having an amino acid sequence that has at least 50% to 60% differences would be useful for treating infinite number of undisclosed disease.

With regard to "chimeric effector domain which is derived from two or more human immunoglobulin heavy chain C_H2 domains including a first human immunoglobulin heavy chain C_H2 domain wherein 2, 3 or 4 amino acids in at least 1 region of the C_H2 domain have been modified to the corresponding amino acids from a second, different, human immunoglobulin heavy chain C_H2 domain" in claim 1 is ambiguous since "two or more human immunoglobulin heavy chain" would encompass IgG2, IgG3 and IgG4. However, not all class of IgG heavy chain and constant domains such as C_H1, C_H3, C_H4 domain of said heavy chain are involved in complement mediated lysis. It is known that IgG3 has a short half life and highly polymorphism, which is not suitable for immune suppressive functions. Further, The claim as written is not clear which amino acid residues within the C_H2 domain of which first human immunoglobulin heavy chain is to be modified from the corresponding amino acids from which second different human immunoglobulin heavy chain.

Riechmann *et al* teach the effector functions of human IgG3 is less effective in both complement and cell-mediated lysis while IgG2 isotype is weakly lytic and IgG4 is non-lytic (See page 326, Heavy-chain constant domains, in particular). Finally, the term "having" in claim 1 is open-ended. It expands the effector domain to include additional amino acid residues at either or both ends. Given the indefinite number of undisclosed amino acid to be added to the effector domain, there is insufficient guidance in the specification as to the structure associated with function of any undisclosed binding molecule for treating any disease. Given the indefinite number of undisclosed binding molecule comprising undisclosed binding specificity, undisclosed chimeric effector domain having multiple amino acids substitution and addition, it is unpredictable which undisclosed binding molecule mentioned above would be useful for any purpose. Since the undisclosed binding molecule in claim 1 is not enabled, it also follows that any binding molecule in the dependent claims 22-15 is not enabled.

With regard to pharmaceutical preparation as recited in claim 30, there is insufficient guidance and a lack of in vivo working example to demonstrate that any binding molecule mentioned above is effective for treating an infinite number of undisclosed diseases. A pharmaceutical preparation in the absence of in vivo data are unpredictable for the following reasons; (1) the binding molecule may be inactivated before producing an effect, i.e. such as proteolytic degradation; (2) the binding molecule may not reach the target area due to metabolic clearance or where the binding molecule has no effect; and (3) other functional properties, known or unknown, may make the binding molecule unsuitable for in vivo therapeutic use, i.e. such as

adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). A pharmaceutical preparation in the absence of in vivo data are unpredictable for the following reasons: (1) the binding molecule may be inactivated before producing an effect, i.e. such as proteolytic degradation; (2) the binding molecule may not reach the target area due to metabolic clearance or where the binding molecule has no effect; and (3) other functional properties, known or unknown, may make the binding molecule unsuitable for in vivo therapeutic use, i.e. such as serum sickness or other adverse side effects prohibitive to the use of such treatment. Given the indefinite number of disease, the lack of guidance and in vivo working examples, further research is required. For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 1-15 and 30 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *any* binding molecule which is a recombinant polypeptide comprising (i) *any* binding domain capable of binding to any target molecule, and (ii) *any* effector domain having *any* amino acid sequence substantially homologous to all or part of *any* constant domain of a human immunoglobulin chain; wherein the binding molecule is capable of binding *any* target molecule without triggering significant complement dependent lysis, or cell mediated destruction of the target, characterized in that the effector domain is capable of specifically biding FcRn and/or FCγRIIb and *any* chimeric effector domain which is derived from *any* two or more human immunoglobulin heavy chain C_H2 domains including *any* first human immunoglobulin heavy chain C_H2 domain wherein

any 2, 3 or 4 amino acids in at least 1 region of the C_H2 domain have been modified to the corresponding amino acids from *any* second, different, human immunoglobulin heavy chain CH2 domain, wherein the region is selected from the 2 discrete regions numbered residues 233-236 and 327-331 in accordance with the EU numbering system, and wherein in each case the human immunoglobulin is selected from IgG1, IgG2, and IgG4, (2) *any* binding molecule mentioned above wherein the first human immunoglobulin is selected from IgG1, IgG2, and IgG4, and the second human immunoglobulin is selected from IgG2 and IgG4, (3) *any* binding molecule mentioned above wherein *any* two amino acids in 1 region of the C_H2 domain are modified to the corresponding amino acids from *any* second human immunoglobulin heavy chain C_H2 domain, (4) *any* binding molecule mentioned above wherein at least *any* two amino acids in each of the two discrete regions of the C_H2 domain are modified to the corresponding amino acids in the corresponding region in *any* second and *any* third human immunoglobulin heavy chain C_H2 domain respectively, (5) *any* binding molecule mentioned above wherein the effector domain shares at least "about 90% sequence identity" with *any* first human immunoglobulin heavy chain C_H2 domain, (6) *any* binding molecule mentioned above wherein comprising *any* human immunoglobulin heavy chain C_H2 domain having *any* one or more amino acids or deletions at the stated positions such as the ones recited in claims 6-7, (7) *any* binding molecule mentioned above wherein the effector domain is selected from *any* G1Δab, *any* G2Δa or *any* G1Δac, (8) *any* binding molecule mentioned above further comprising modifications to render the molecule "substantially null allotypic", (9) *any* binding molecule mentioned above wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparison with *any* first or second human immunoglobulin heavy chain C_H2 domain, (10) *any* binding molecule mentioned above wherein the effector domain has retained an affinity for FcγRIIb, (11) *any* binding molecule mentioned above wherein the binding domain derives from *any* different source to the effector domain, (12) *any* binding molecule mentioned above wherein the binding domain is selected from the binding site of *any* antibody, any enzyme, any hormone, any receptor, any cytokine or any antigen any ligand or *any* adhesion molecule, (13) *any* binding molecule mentioned above wherein the binding site is *any* capable of *any* of binding to any RhD antigen, *any* HPA alloantigen of platelet, *any* neutrophil antigen, *any* T cell receptor, *any* integrin, *any* GMB collagen, *any* Der P1, *any* HPA-1a, *any* VAP-1, *any* laminin, *any* Lutheran, *any* platelet glycoprotein VI, *any* platelet glycoprotein Ia/IIa, and (14) *any*

pharmaceutical preparation comprising *any* binding molecule mentioned above plus a pharmaceutically acceptable carrier for treating any disease.

The specification discloses only binding molecules which are recombinant antibodies wherein each recombinant antibody comprises a binding domain capable of binding to CAMPATH-1 (CD52) or FOG-1 (RhD antigen on RBC) and variant of human IgG1 constant region which incorporate IgG2 residues in the region 233-236 and/or IgG4 residues at positions 327, 330 and 331 into the corresponding amino acid residues of IgG1 based on the European Union numbering system. The first region comprises residues 233-236, which is part of the hinge link or lower hinge region of the C_H2 domain while the second region 327, 330 and 331 is the N-terminal end of the CH2 domain. In the G1Δab mutation of SEQ ID NO: 1, the E at position 233 of IgG1 is substitute for P from IgG2, the L at position 234 of IgG1 is substitute for V from IgG2, the L at position 235 is substituted for A from IgG2, Since IgG2 has a deletion at 236 where the other class of IgG has G, the mutation at 236 is omitted (no residue) or substitute for G at 236, the A at 327 of IgG1 is substitute for G from IgG4, The A at 330 of IgG1 is substitute for S from IgG4 and the P at 331 of IgG1 is substitute for S from IgG4. For the G2Δa mutation of SEQ ID NO: 2, E is changed to P at position 233, L to V at position 234, L to A at position 235, a deletion at position 236, A to G at position 327, A to S at position 330 and P to S at position 331. For G1Δac mutation of SEQ ID NO: 3, E is changed to P at position 233, L to V at position 234, L to A at position 235, G remains the same at position 236, A to G at position 327, A to S at position 330 and P to S at position 331. The said binding molecules of SEQ ID NO: 1, 2 and 3 wherein the effector domain has a reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1. The said binding molecules of SEQ ID NO: 1, 2 and 3 wherein the effector domain has retained an affinity for FcγRIIb.

With the exception of the specific binding molecule mentioned above wherein the binding domain is FOG-1 and CAMPATH-1 and the effector domain selected from the group consisting of SEQ ID NO: 1, SEQ IN NO: 2 and SEQ ID NO: 3 for in vitro screening of the killing of PBMC by complement lysis with CAMMPATH-1 or the killing of RBD by ADCC with Fog-1 associated with fetal thrombocytopenia by way of assessing directly or indirectly through inability to trigger monocyte chemiluminescence, there is insufficient written description about the structure associated with function of *any* binding molecule mentioned above, and *any* pharmaceutical preparation comprising *said* binding molecule for treating *any* disease. Further,

given that only three specific combination of mutations in the specific amino acid residues within the specific regions of the human immunoglobulin heavy chain C_H2 domain which have demonstrated the desired functions such as reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis while still retained an affinity for FcγRIIb, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 1, 4, 9, 13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "chimeric effector domain…IgG4" in claim 1 is indefinite and ambiguous. The claim as written is unclear as to the amino acid substitution within the effector domain of which specific class of IgG have been modified to the corresponding amino acids from which second, different human IgG heavy chain C_H2 domain. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The recitation of "in each case" in claim 1 is indefinite and ambiguous. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

The recitation of "and third human immunoglobulin heavy chain" in claim 4 has no antecedent basis in base claim 1. Base claim 1 requires first and second different human immunoglobulin heavy chain C_H2 domain.

The recitation of "modifications" in claim 9 is ambiguous and one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. Other than the amino acid substitution, and/or deletion at the specified amino acid residues, it is not clear what are the additional modifications applicant intends to claim.

The recitation of "substantially null allotypic" in claim 9 is ambiguous and one of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention. The specification does not defined what is meant by "substantially null allotypic".

The recitation of "binding site" of an antibody in claim 13 is indefinite and ambiguous because the binding domain of an antibody could be the hypervariable region of the antibody or the amino acid sequence to which the antibody binds. Clarification is required.

Claim 15 contains the trademark/trade name "CAMPATH-1". Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe the binding domain of the binding molecule and, accordingly, the identification/description is indefinite.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-3, 5-7, 11-15 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Greenwood *et al* (Eur J Immunol 23: 1098-1104, 1993; PTO 892).

Greenwood *et al* teach a binding molecule such as chimeric recombinant antibodies DS1141, DS4414, DS4114 comprising (i) a binding domain capable of binding a target molecule such as CAMPATH-1 antigen (CD52) and (ii) an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human immunoglobulin heavy chain wherein the reference binding molecule is capable of binding to the target molecule without significant complement mediated lysis or triggering cell mediated destruction of the target (ADCC) and the reference chimeric effector domain is derived from human immunoglobulin heavy chain CH2 domain from IgG1, and IgG4 (See Figs 1-4, in particular) and the reference chimeric effector domain includes Y to F at position 296. Greenwood *et al* teach the structural

requirements for effector function is located in the C-terminal half of the CH2 domain (residues 234, 238 and the hinge-link region from 300-331 (See page 1103, Fig 5, in particular). Greenwood *et al* teach four residues could be responsible for the failure of lack of ADCC: Tyr at 296 in IgG1 vs Phe in IgG4, Ala in 327 versus Gly in IgG4, Ala in 330 in IgG1 versus Ser in IgG4 and Pro at 331 in IgG1 to Ser in IgG4 (See Fig 5, page 1104, column 1, first full paragraph, in particular). The reference binding molecule wherein the first human immunoglobulin is IgG1 and the second human immunoglobulin is IgG4 (See Fig 1, in particular). The reference binding molecule wherein 2 amino acids in 1 region such as the C terminal half of the C_H2 domain are modified to the corresponding amino acids from a second human immunoglobulin heavy C_H2 domain such as IgG4 (See Fig 5, in particular).). The reference binding molecule wherein the effector domain shares at least about 90% identity with the wild type human immunoglobulin heavy chain CH2 domain since it has only one, two or maximum four mutations in the C_H2 domain compared with the wild type. The reference binding molecule comprising a human immunoglobulin heavy chain C_H2 domain having A at position 235, G position 327, S at positions 330 and 331(See Figs 1 and 5, in particular). The reference binding molecule comprising a human immunoglobulin heavy chain CH2 domain having a block of amino acids such as G position 327, S at positions 330 and 331. (See Figs 1 and 5, in particular). The reference binding molecule wherein the binding domain is derived from a different source such as rat or chimeric humanized CAMPATH-1 antibodies to the effector domain (See page 1099, Materials and methods, in particular). The reference binding molecule is an antibody wherein the binding domain is capable of binding to a glycoprotein such as CAMPATH-1 (CD52) (See page 1099, Materials and methods, Introduction in particular). Greenwood *et al* further teach a pharmaceutical acceptable carrier such as IMDM for a pharmaceutical preparation comprising the reference binding molecule (See page 1099, column 2, ADCC, in particular). Greenwood *et al* teach IgG1 is the most potent isotype in ADCC, with IgG3 somewhat less effective and IgG2 and IgG4 ineffective. The residues in the hinge-link region (233-238) are crucial to binding to the high affinity receptor FcγRI and the binding site for FcγRIII is overlapping this region (See page 1099, column 1, first paragraph, in particular). Greenwood *et al* teach it is possible to improve the antibody effector functions of any antibody by construction of novel antibodies that either possess ADCC or complement mediated killing or the lack thereof for therapy such as donor heterogeneity (See abstract, page 1099, column 1, second paragraph, in particular). Claim 11 is included in this rejection because the reference binding molecule inherently still binds to the

FcγIIb, which is one of the low affinity receptor, since it doesn't trigger cellular response. Thus, the reference teachings anticipate the claimed invention.

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1, 4, 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwood *et al* (Eur J Immunol 23: 1098-1104, 1993; PTO 892) in view of Mogan *et al* (Immunology 86: 319-324, 1995, PTO 1449) or Chappel *et al* (Proc Nat. Acad. Sci. USA 88: 9036-40, 1991; PTO 1449) or Cole *et al* (Immunology 159: 3613-21, 1997 ; PTO 1449).

The teachings of Greenwood *et al* have been discussed supra.

The claimed invention as recited in claim 1 differs from the reference only by the recitation that the human immunoglobulin is IgG2.

The claimed invention as recited in claim 4 differs from the reference only by the recitation that at least two amino acids in each of the 2 discrete regions of the CH2 domain are modified to the corresponding amino acids in the corresponding region in second and third human immunoglobulin heavy chain CH2 domain respectively.

The claimed invention as recited in claim 8 differs from the reference only by the recitation that the effector domain is selected from G1Δab (223P, 234V, 235A, 236 no residues, 327G, 330S, and 331S), G2Δa (223P, 234V, 235A, 236 no residues, 327G, 330S, and 331S), and G1Δac (223P, 234V, 235A, 236G, 327G, 330S, and 331S).

The claimed invention as recited in claim 10 differs from the reference only by the recitation that the effector domain has reduced affinity for FcγRI, FcγRIIa or FcγRIII and a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1.

Mogan *et al* (PTO 1449) teach a binding molecule such as G1[L235A] which is a recombinant polypeptide such as recombinant immunoglobulin comprising (i) a binding domain capable of binding a target molecule such as HLA-DR and (ii) an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human immunoglobulin heavy chain wherein the reference binding molecule is capable of binding to the target molecule without triggering significant complement dependent lysis or cell mediated destruction of the target (Table 2, page 321, in particular). The reference chimeric effector domain having Leu at position 235 in the C_H2 domain of IgG1 changes to Ala (A) taken from IgG2 still capable of binding to FCRn such as FcγRI but the binding is reduced by about 100 fold. The reference teaches changing Leu at position 235 to Glu change in human IgG4 abolished complement lysis (no killing of target) while Ala at 235 permitted low levels of killing (See page 322, column 1, last paragraph, bridging column 2, in particular).

Chappel *et al* (of record, 1449) teach a binding molecule which is a recombinant polypeptide such as recombinant immunoglobulin comprising (i) a binding domain capable of binding a target molecule such as dinitrophenyl and (ii) an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human immunoglobulin heavy chain wherein the reference binding molecule is capable of binding to the target molecule and the reference chimeric effector domain is derived from human immunoglobulin heavy chain C_H2 domain from IgG1, IgG2 and IgG4 wherein 2 amino acids in region 231-238 of the C_H2 domain have been modified such as substitution and/or deletion to the corresponding amino acids from a different human immunoglobulin heavy chain C_H2 domain such as IgG2 and IgG4 (See Materials and Methods, Table 2, in particular). The reference human immunoglobulin is selected from IgG1, IgG2 and IgG4 (See Table 2, in particular). The reference binding molecule such as IgG2-2-1 hybrid immunoglobulin binds to the FcγRI on U937 cells (See page 9038, column 1, in particular). The reference binding molecule wherein progressive substitution such as two, three or four amino acids in 1 region such as 231-238 of the C_H2 domain of IgG1, IgG2 or IgG4 are modified to the corresponding amino acids from a second (wild type) human immunoglobulin heavy chain C_H2 domain (See page 9039, Table 2, column 1, Table 4, in particular). The

reference binding molecule wherein the effector domain shares at least about 90% identity with the wild type human immunoglobulin heavy chain CH2 domain since it has only one, two or maximum four mutations in the CH2 domain compared with the wild type. The reference binding molecule comprises a human immunoglobulin heavy chain CH2 domain having one or more amino acids substitution from E to P at position 233, L to V at position 234, L to A at position 235, no residue or glycine at position 236 in accordance with the EU numbering system (See page 9038, column 2, in particular). The reference binding molecule wherein the binding domain is the binding site of an antibody (See page 3097, column 1, in particular). Chappel *et al* teach reciprocal shuffling of the C_H2 domains between IgG1 and IgG2 subclass unambiguously revealed that the FcγRI binding is located in the C_H2 domain and effector function can be abolish in all IgG1 containing IgG C_H2 domain (See page 9039, column 2, last paragraph, in particular).

Cole *et al* (of record, Immunology 159: 3613-3621; PTO 1449) teach a binding molecule which is a recombinant polypeptide comprising a binding domain capable of binding to a target molecule such as a T cell receptor and an effector domain having an amino acid sequence substantially homologous to part of a constant domain of a human heavy chain wherein the effector domain comprises a human immunoglobulin heavy chain of IgG2 having at least 2 amino acids at position 234 and 235 have been modified to V and A, respectively (See page 3615, Table 1, in particular). The said effector domain is capable of specifically binding to FcγIIb, and is derived from two or more human immunoglobulin heavy chain C_H2 domains from IgG2 (See page 3614, Materials and Methods, page 3617-3619, in particular). Cole *et al* teach IgG2 variant chimeric anti-CD3 having Ala at 234, Ala or Glu at 235, Gly or no residue at 236 has low affinity for FcγRI and FcγRII, and is ineffective in mediating cytotoxicity against target cells (See Table 1, page 3617, column 2, page 3620, column 1, in particular), which is useful for retaining potent immunosuppressive properties (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the human immunoglobulin heavy chain C_H2 domain of the IgG1 within the binding molecule as taught by Greenwood *et al* for the A at position 235 or the Glu at position 235 as taught by Mogan *et al* or the P at position 233, V at position 234, A at position 235, no residue or glycine at position 236 in accordance with the EU numbering system as taught by Chappel *et al* or the V at position 234 and A at position 235 as taught by Cole *et al* for a binding molecule comprising a human immunoglobulin heavy chain CH2 domain having at least two amino acids in each of the 2 discrete regions of the C_H2 domain are modified to the

corresponding amino acids in the corresponding region in second and third human immunoglobulin heavy chain C_H2 domain such as IgG2 and IgG4 wherein the effector domain has reduced affinity for FcγRI, or FcγRIII and a reduced ability to mediate complement lysis by comparing to the unmodified human immunoglobulin heavy chain C_H2 domain of IgG1 as taught by Greenwood *et al,* Mogan *et al,* Chappel *et al* and Cole *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Mogan *et al* teach substituting Leu at position 235 of IgG1 for Glu of human IgG4 abolished complement lysis (no killing) while Ala at 235 permitted low levels of killing (See page 322, column 1, last paragraph, bridging column 2, in particular). Chappel *et al* teach reciprocal shuffling of the C_H2 domains between IgG1 and IgG2 subclass and having one or more amino acids substitution from E to P at position 233, L to V at position 234, L to A at position 235, no residue or glycine at position 236 in accordance with the EU numbering system can abolish effector function in the all IgG1 containing IgG C_H2 domain (See page 9039, column 2, last paragraph, in particular). Cole *et al* teach IgG2 variant having Ala at 234, Ala or Glu at 235, Gly or no residue at 236 has low affinity for FcγRI and FcγRII, and is ineffective in mediating cytotoxicity against target cells (See page 3617, column 2, page 3620, column 1, in particular), which is useful for retaining potent immunosuppressive properties (See abstract, in particular). Greenwood *et al* teach it is possible to improve the antibody effector functions of any antibody by construction of novel antibodies that either possess ADCC or complement mediated killing or the lack thereof for therapy such as donor heterogeneity (See abstract, page 1099, column 1, second paragraph, in particular). Claims 8 is included in this rejection because Greenwood *et al* teach substituting A at 325 (325A), G at 327 (327G), S at 330 and 331 (330S, and 331S) while Mogan *et al* teach substitution A at 325, Chappel *et al* teach substituting P at position 233, V at position 234 and A at position 235 and Cole *et al* teach IgG2 variant having Ala at 234, Ala or Glu at 235, Gly or no residue at 236 has low affinity for FcγRI and FcγRII, and is ineffective in mediating cytotoxicity against target cells (See Table 1, page 3617, column 2, page 3620, column 1, in particular). From the combined teachings of Greenwood *et al,* Mogan *et al* Cole *et al* and Chappel *et al,* it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

19. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwood *et al* (Eur J Immunol 23: 1098-1104, 1993; PTO 892) in view of WO 95/05468 publication (Feb 1995, PTO 892).

The teachings of Greenwood *et al* have been discussed supra.

The claimed invention as recited in claim 9 differs from the reference only by the recitation that the binding molecule further comprising modifications to render the molecule substantially null allotypic.

The WO 95/05468 publication teaches binding molecule such as CAMPATH-1 recombinant antibodies which has a first amino acid sequence comprising a domain with an ability to bind to a target and a second amino acid sequence comprising part or all of a human immunoglobulin heavy chain having an allotypic determinant associated with a desired effector function (See abstract, in particular). The WO 95/05468 publication teaches aglycosylated mutation having Asn changes to Ala at position 297 of the human IgG1 domain abolishes N-linked glycosylation and the mutant fails to mediate complement lysis (See page 12, line 14-17, page 17, line 16-19, page 18, lines 22-25, page 19, lines 20-22, in particular). The WO 95/05468 publication teaches allotypic polymorphism is to a certain extend responsible for different effector functions and one can moderate the functions of one subsclass by introducing mutations at positions homologous to given alleles of another subclass, then the activity in complement activation of the mutant should be reduced compared to the wild type (See page 28, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Asn at position 297 to Ala of the human IgG1 domain to abolish N-linked glycosylation as taught by the WO 95/05468 publication in addition to having A at position 235, G position 327, S at position 330 and 331 as taught by Grenwood *et al* (See Figs 1 and 5, in particular) for a binding molecule comprising a binding domain and an effector domain wherein the binding molecule is capable of binding to the target without triggering significant complement dependent lysis or cell mediated destruction of the target associated with allotypic polymorphism as taught by the Grenwood *et al* and the WO 95/05468 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 95/05468 publication teaches allotypic polymorphism is to a certain extend responsible for different effector functions and one can moderate the functions of

one subsclass by introducing mutations at positions homologous to given alleles of another subclass, then the activity in complement activation of the mutant should be reduced compared to the wild type (See page 28, in particular) and further mutation by site-directed mutagenesis in any C_H2 domain would render the molecule substantially null allotypic.

20. Claims 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenwood *et al* (Eur J Immunol 23: 1098-1104, 1993; PTO 892) in view of US Pat No 5,831,063 (Nov 1998, PTO 892).

The teachings of Greenwood *et al* have been discussed supra.

The claimed invention as recited in claim 15 differs from the reference only by the recitation that the binding domain is FOG1.

The '063 patent teaches recombinant human monoclonal anti-Rh(D) antibodies and a method of making said antibody that binds to FOG1 on human red blood cell (See abstract, column 2, line 41, in particular). The '063 patent teaches the reference antibody is useful for both therapy for passive immunization to prevent hemolytic disease of the newborn and diagnosis (column 4, lines 14-23, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the binding domain of CAMPATH-1 as taught by Greenwood *et al* for the binding domain of FOG-1 as taught by the '063 patent for a binding molecule which is a recombinant polypeptide comprising a binding domain capable of binding to FOG-1, which is the RhD antigen on red blood cell, and an effector domain having an amino acid sequence substantially homologous to all or part of the a constant domain of a human immunoglobulin heavy chain as taught by Greenwood *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '063 patent teaches the antibody is useful for both therapy for passive immunization to prevent hemolytic disease of the newborn and diagnosis (column 4, lines 14-23, in particular).

21. No claim is allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

23. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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